Dietary Factors and the Risk of Pancreatic Cancer: A Case-Control Study in Shanghai, China[1]

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Abstract

In Shanghai, China, age-adjusted incidence rates for pancreatic cancer have increased steadily, beginning in the early 1970s. To examine the effects of diet on this cancer, a population-based case-control study was conducted. Cases (*n* = 451) were permanent residents of Shanghai, 30–74 years of age, newly diagnosed with pancreatic cancer between October 1, 1990 and June 30, 1993. Deceased cases (19%) were excluded from the study. Controls (*n* = 1552) were selected among Shanghai residents, frequency matched to cases by gender and age. Information on usual adult dietary intake was obtained by trained interviewers in person, using a food frequency questionnaire. Dietary associations were measured by odds ratios and 95% confidence intervals. Risks of pancreatic cancer were inversely associated with consumption of vegetables (*P* for trend among men = 0.03; among women = 0.15) and fruits (*P* among men = 0.02; among women = 0.08). Reductions in risk were related also to intake of dietary fiber and micronutrients abundant in plant sources, such as vitamins C and E and carotene. There was also an inverse association with egg consumption (*P* for trend among men = 0.08; among women = 0.001). No consistent positive associations were observed with intake of other food groups, including preserved animal foods, fresh red meat, organ meat, poultry, and staple foods. On the other hand, risks increased with frequency of consumption of preserved vegetables and foods that were deep fried, grilled, cured, or smoked, providing clues to the possible role of nitrosamines, polycyclic aromatic hydrocarbons, and heterocyclic aromatic amines. The inverse associations observed with intake of dietary fat and protein in our study were unexpected, although these findings were based on consumptions well below the average intake in Western countries, where most previous studies on pancreatic cancer were conducted. Our results suggest that dietary variations have contributed little to the rising trends of pancreatic cancer in Shanghai. However, given the improving food availability and changing dietary patterns in China, further study of dietary and nutritional risk factors for pancreatic cancer appears warranted.

Introduction

Diet is believed to play a role in pancreatic carcinogenesis (1), although the specific components and mechanisms remain unclear. Several studies have reported inverse associations with consumption of fruits and vegetables (2–8) and positive associations with intake of beef, pork, poultry, or fish (3–5, 9–11). Elevated risks of pancreatic cancer have also been linked to intake of eggs and dairy products (5, 12, 13), butter and margarine (2, 14), and rice and white bread (2, 6, 10, 14). Less consistent are the associations reported with specific dietary nutrients. Increased risks have been related to high intake of fat (15–17) and unsaturated fat (18) in some studies but not others (2, 19–21). An excess risk has been associated in some studies with high intake of carbohydrates (22–24).

Age-adjusted incidence rates of pancreatic cancer in Shanghai, China, have increased steadily between 1972–1974 and 1987–1989 (25). In 1987–1989, the average annual rates were 6.1 and 4.2 per 100,000 and ranked eighth and ninth among cancer incidence in men and women, respectively. To identify the risk factors for pancreatic cancer in Shanghai, we undertook a large population-based case-control study. In an earlier report, we found elevated risks with cigarette smoking but not alcohol consumption, suggesting that the increasing prevalence of smoking has contributed to the rising trend of pancreatic cancer (26). In addition, the living standard among Shanghai residents, including access to medical care and the availability of a variety of foods, has improved since the early 1970s (27). In this report, we present the risks of pancreatic cancer associated with dietary and nutritional factors.

Materials and Methods

Methods for this population-based case-control study of gastrointestinal cancers (pancreas, esophagus, colon, and rectum) have been described in detail elsewhere (26, 28). Briefly, pancreatic cancer cases newly diagnosed between October 1, 1990, and June 30, 1993, were identified through a rapid reporting system. Cases were 30–74 years of age and permanent residents in urban Shanghai. Of the 577 eligible patients, 451 (78.2%) were interviewed. Study cases were confirmed by histopathology (37%), surgery with gross but not microscopic pathology (20%), or computed tomography scan/ultrasound (43%). Excluded from the study were 109 cases who died

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Table 1 ORs[a] and 95% CIs of pancreatic cancer in relation to quartiles of food group consumption by sex, Shanghai, China, 1990–1993

		Men				*P* for trend	Women				*P* for trend
		Q1[b] (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
Preserved vegetables	OR	1.00	1.16	1.65	1.37	0.07	1.00	1.54	2.17	3.07	<0.001
	95% CI		(0.74–1.82)	(1.07–2.53)	(0.89–2.11)			(0.85–2.80)	(1.22–3.84)	(1.77–5.33)	
Preserved animal foods	OR	1.00	0.82	1.05	0.82	0.63	1.00	1.38	0.87	0.88	0.31
	95% CI		(0.53–1.28)	(0.70–1.59)	(0.53–1.26)			(0.85–2.26)	(0.51–1.48)	(0.52–1.51)	
Fresh red meats	OR	1.00	0.64	0.76	0.73	0.24	1.00	1.34	0.83	1.24	0.86
	95% CI		(0.42–0.99)	(0.50–1.15)	(0.47–1.12)			(0.81–2.21)	(0.47–1.43)	(0.73–2.13)	
Organ meats	OR	1.00	1.10	1.30	0.82	0.63	1.00	0.64	1.51	1.21	0.27
	95% CI		(0.70–1.81)	(0.90–1.91)	(0.67–1.31)			(0.38–1.41)	(0.91–2.34)	(0.72–1.80)	
Poultry	OR	1.00	1.23	0.97	0.93	0.46	1.00	0.85	0.66	1.06	0.96
	95% CI		(0.81–1.87)	(0.63–1.51)	(0.60–1.44)			(0.51–1.42)	(0.39–1.13)	(0.63–1.78)	
Fish	OR	1.00	1.19	1.32	1.29	0.23	1.00	0.61	1.19	0.94	0.59
	95% CI		(0.75–1.87)	(0.85–2.04)	(0.83–2.01)			(0.35–1.06)	(0.73–1.96)	(0.56–1.58)	
Eggs	OR	1.00	0.77	0.77	0.67	0.08	1.00	0.79	0.56	0.46	0.001
	95% CI		(0.51–1.18)	(0.50–1.17)	(0.44–1.03)			(0.49–1.28)	(0.34–0.93)	(0.27–0.79)	
Staple foods	OR	1.00	1.00	1.10	1.41	0.10	1.00	0.91	0.70	1.10	0.86
	95% CI		(0.60–1.54)	(0.70–1.70)	(0.90–2.11)			(0.50–1.41)	(0.41–1.31)	(0.72–1.80)	

[a] Adjusted for age, income, smoking, green tea drinking (females only), and response status.
[b] Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

before participation, 11 who moved away, and 6 who refused interview.

Controls were randomly selected from the general Shanghai population, frequency matched to the expected age (5-year category) and sex distribution of the 4 gastrointestinal cancers combined in the overall study. Personal identification cards from the Shanghai Resident Registry were used to select controls. The cards contain information on name, address, date of birth, gender, and other demographic factors. Two random numbers (a 4-digit number for locating a drawer and a 3-digit number for locating a personal identification card within the drawer) were generated to select each control. For each control chosen, an alternate control was also selected. If the first control could not be interviewed, the alternate was enrolled. A total of 1552 controls were interviewed, of whom, 240 (15.4%) were alternates.

Each subject was interviewed in person by trained interviewers. Because some cases and controls were too weak to withstand a complete interview, family members were allowed to assist in responding to the questionnaire. A structured questionnaire was used to obtain information on demographic and residential characteristics, diet, consumption of smoking, alcohol and other beverages, physical activity, and occupation. Dietary intake included 86 food items commonly consumed in Shanghai. Frequency and amount in liang (1 liang = 50 g) of usual intake 5 years before diagnosis for cases and 5 years before the date of interview for controls were ascertained. The consumption of seasonal foods was ascertained within season. Because a large number of vegetables and fruits in China were only available seasonally, the average monthly intake of those foods was calculated by weighting the length of time that the food was available each year. Frequency of intake of selected food groups was examined by combining intake of related food items (see Appendix 1 for a listing of the food groups and the items in these groups). In addition, preference for selected cooking methods and other dietary habits were obtained.

Monthly intake of selected nutrients was computed using information based on the Chinese food composition tables (29). Total dietary intake of each nutrient was calculated by summing the amount of intake from all food items, which were individually estimated by multiplying the nutrient content of the reported frequency by the amount of intake for each food item. Use of vitamin supplements was uncommon and, therefore, not ascertained in this study.

For analysis, consumption of foods and nutrients was divided into quartiles based on the distribution among controls, separately for men and women, with approximately equal numbers of controls in each intake stratum (see Appendix 2 for cutpoints for food items and food groups and Appendix 3 for nutrient quartiles). Statistical analyses were conducted using a stratified method and logistic regression for evaluation of multivariate relationships. Risks in relation to quartile of intake of foods and nutrients were measured by ORs[5] and 95% CIs (30). Dose-response relationships for the categorical variables were examined. All ORs were adjusted for age, monthly family per capita income, number of cigarettes per day, and whether the interview was assisted by next of kin (response status). Among women, ORs were further adjusted for green tea drinking because it was a confounding factor identified in our data. For nutrient analysis, ORs were also adjusted for total caloric intake (31). Further adjustment for other potential confounding factors, such as education, level of physical activity, body mass index, and history of chronic pancreatic diseases and diabetes, did not alter the main effects. All analyses were conducted separately for men and women.

Results

Pancreatic cancer cases tended to be older than controls (median age for cases was 63 and 62 among men and 65 and 61 among women, respectively) because of frequency match using the age distribution of the combined cases of the four gastrointestinal cancers. The cancer cases have higher family income

[5] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 ORs[a] and 95% CIs of pancreatic cancer in relation to quartiles of consumption of fresh vegetables and fruits by sex, Shanghai, China, 1990–1993

		Men				P for trend	Women				P for trend
		Q1[b] (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
All vegetables	OR 95% CI	1.00	0.84 (0.56–1.25)	0.61 (0.42–0.93)	0.68 (0.45–1.03)	0.03	1.00	0.95 (0.58–1.55)	0.88 (0.53–1.45)	0.67 (0.39–1.14)	0.15
Dark green leafy vegetables	OR 95% CI	1.00	0.75 (0.49–1.14)	0.83 (0.54–1.28)	0.84 (0.54–1.32)	0.61	1.00	0.88 (0.53–1.45)	1.02 (0.62–1.67)	0.96 (0.56–1.65)	0.82
Cruciferous vegetables	OR 95% CI	1.00	0.91 (0.61–1.38)	0.87 (0.57–1.33)	0.79 (0.52–1.21)	0.27	1.00	0.80 (0.47–1.36)	1.32 (0.80–2.19)	1.07 (0.64–1.78)	0.41
Legumes	OR 95% CI	1.00	1.12 (0.74–1.69)	0.84 (0.55–1.30)	0.94 (0.61–1.44)	0.48	1.00	1.07 (0.66–1.72)	0.62 (0.37–1.10)	0.55 (0.32–0.95)	0.007
Soybean products	OR 95% CI	1.00	1.01 (0.65–1.55)	1.28 (0.85–1.94)	0.90 (0.58–1.39)	0.93	1.00	0.85 (0.51–1.44)	0.82 (0.49–1.37)	0.79 (0.47–1.33)	0.38
All fruits	OR 95% CI	1.00	0.99 (0.66–1.49)	0.68 (0.45–1.05)	0.66 (0.43–1.01)	0.02	1.00	0.68 (0.41–1.10)	0.77 (0.46–1.30)	0.58 (0.34–1.00)	0.08
Oranges	OR 95% CI	1.00	1.08 (0.72–1.63)	0.68 (0.45–1.01)	0.65 (0.42–0.99)	0.01	1.00	0.80 (0.46–1.39)	0.89 (0.56–1.42)	0.58 (0.34–0.99)	0.08
Bananas	OR 95% CI	1.00	0.70 (0.47–1.02)	0.65 (0.41–1.02)	0.58 (0.38–0.91)	0.01	1.00	0.61 (0.38–0.98)	0.66 (0.38–1.13)	0.45 (0.26–0.78)	0.007
Apples	OR 95% CI	1.00	0.77 (0.51–1.17)	0.85 (0.54–1.35)	0.69 (0.46–1.04)	0.11	1.00	0.78 (0.47–1.29)	0.87 (0.52–1.46)	0.59 (0.33–1.05)	0.12
Other fruits	OR 95% CI	1.00	0.89 (0.59–1.36)	0.85 (0.57–1.27)	0.68 (0.44–1.03)	0.07	1.00	0.80 (0.48–1.33)	0.74 (0.42–1.33)	0.85 (0.52–1.38)	0.55

[a] Adjusted for age, income, smoking, green tea drinking (females only), and response status.
[b] Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

than controls [median family per capita income (yuan/month) was 43 and 39 among men and 43 and 34 among women, respectively]. More cases were current smokers (70% men, 15% women) than were controls (66% men, 13% women). Among women, controls (23%) were more likely to drink green tea regularly than cases (19%); however, among men, the proportion of regular green tea drinkers was similar for cases (63%) and controls (62%). In addition, the next of kin assisted a higher proportion of interviews with cases (43% men, 40% women) than controls (13% men, 7% women).

Risk of pancreatic cancer rose significantly with frequency of consumption of preserved vegetables among women, with ORs increasing from 1.54 (95% CI = 0.85–2.80) in the second quartile of intake to 2.17 (95% CI = 1.22–3.84) and 3.07 (95% CI = 1.77–5.33) in the third and fourth quartiles, respectively (Table 1). Slightly elevated risks (OR = 1.16–1.37) were associated with intake of preserved vegetables among men, but the trend was not smooth. Further adjustment for vitamin C intake increased slightly the ORs associated with preserved vegetables (OR = 3.26 for women and OR = 1.49 for men in the highest quartile). No consistent associations were observed with consumption of preserved animal foods, fresh red meat, organ meat, and poultry among men or women. A nonsignificant 30–40% excess risk was observed among men with above-median intake of fish or with the highest quartile of intake of staple foods, but no association was seen in women. On the other hand, an inverse association was observed with increasing frequency of egg consumption in both sexes. Men in the highest quartile of egg consumption had a 30% reduction in risk (OR = 0.67; 95% CI = 0.44–1.03), whereas women had a 50% reduction (OR = 0.46; 95% CI = 0.27–0.79).

Consumption of vegetables and fresh fruits was inversely associated with risks of pancreatic cancer (Table 2). Among men, ORs decreased from 0.84 in the second quartile of total vegetable intake to 0.61 and 0.68 in the third and fourth quartiles, respectively (P for trend = 0.03). Among women, ORs also declined with increasing consumption of vegetables ($P = 0.15$), dropping 30% in the highest quartile. The decrease in risk with amount of consumption was most notable for cruciferous vegetables among men and for legumes and soybean products among women. The inverse associations with individual vegetables, however, were less apparent, and few had reached statistical significance, partly due to the small variations in the consumption of some common vegetables, such as bok choy and cabbage (data not shown). No single vegetable appeared to be a dominant contributor to the overall inverse association with vegetable intake. Risks declined also with increasing consumption of fruits in both sexes. In the highest quartile of fruit intake, men had a 30% lowered risk (P for trend = 0.02), whereas women had a 40% lowered risk (P for trend = 0.08). Similar reductions in risk were seen for specific fruits (oranges/tangerines, bananas, apples, and other fruits).

Risks of pancreatic cancer rose with increasing frequency of consumption of foods that were deep fried, grilled, cured, or smoked, although the trend was significant only for grilled foods among men ($P = 0.02$) and cured foods among women ($P = 0.0008$) (Table 3). Among men, frequent consumption of grilled foods was associated with a 4-fold risk (OR = 4.08; 95% CI = 1.52–11.0). Among women, frequent consumption of cured foods was associated with a 2-fold risk (OR = 2.14; 95% CI = 1.29–3.56).

Total caloric intake was inversely related to risk of pancreatic cancer, but the trends were not significant (Table 4). On average, carbohydrates accounted for 67% of the total caloric

Table 3 ORs[a] and 95% CIs of pancreatic cancer in relation to preference for special processed foods by sex, Shanghai, China, 1990–1993

	Men			Women		
	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
Deep fried foods						
Never/seldom	151/543	1.00		127/472	1.00	
Sometimes	70/188	1.37	(0.96–1.95)	33/129	1.16	(0.72–1.87)
Frequently	40/116	1.37	(0.89–2.12)	24/79	1.30	(0.75–2.25)
P for trend			0.06			0.32
Grilled foods						
Never/seldom	236/786	1.00		172/642	1.00	
Sometimes	15/52	1.13	(0.60–2.11)	11/30	1.23	(0.55–2.76)
Frequently	10/9	4.08	(1.52–11.0)	1/8	0.58	(0.06–5.03)
P for trend			0.02			1.00
Cured foods						
Never/seldom	163/591	1.00		102/456	1.00	
Sometimes	50/160	1.18	(0.80–1.74)	46/141	1.77	(1.14–2.76)
Frequently	47/96	1.40	(0.91 –2.14)	36/82	2.14	(1.29–3.56)
P for trend			0.10			0.0008
Smoked foods						
Never/seldom	250/813	1.00		172/642	1.00	
Sometimes	7/29	0.85	(0.35–2.04)	4/20	0.63	(0.19–2.01)
Frequently	4/5	1.67	(0.34–8.15)	2/2	4.86	(0.44 –53.8)
P for trend			0.83			0.84

[a] Adjusted for age, income, smoking, green tea drinking (females only), and response status.

intake, whereas fat and protein accounted for 21 and 12% of the total calories, respectively. After adjusting for total caloric intake, no association was observed with the fraction of calories from carbohydrates (Table 4). On the other hand, risks decreased with increasing percentages of calories from fat (P for trend = 0.02 for men and 0.21 for women) and from protein (P = 0.002 for men and 0.05 for women). Relative to those in the lowest quartiles, a 40–50% reduction in risk was seen among men in the highest quartile of fat (OR = 0.58; 95% CI = 0.36–0.93) and protein (OR = 0.51; 95% CI = 0.33–0.79) intake. The corresponding ORs among women were 0.77 (95% CI = 0.44–1.34) for fat and 0.55 (95% CI = 0.32–0.95) for protein. It should be noted that a large proportion of food sources contributing to fat were different from those comprising the protein group. The inverse associations were similar for saturated fat and mono- and polyunsaturated fats. The associations also were similar for plant and vegetable protein (data not shown).

Significant inverse associations were found between risk of pancreatic cancer and dietary intake of vitamin C, carotene, vitamin E, retinol, and dietary fiber in both men and women (Table 5). Intake of vitamin C and carotene was strongly correlated (pearson correlation coefficients, r = 0.8; P = 0.0001), whereas the effects of vitamins C and E, retinol, and dietary fiber were independent of one another.

Table 4 ORs and 95% CIs of pancreatic cancer in relation to intake of total calories and percentage of calories from carbohydrate, fat and protein, Shanghai, China, 1990–1993

(Quartile)	Men		Women	
	OR	95% CI	OR	95% CI
Total calories[a]				
Q1[b]	1.00		1.00	
Q2	0.79	(0.52–1.19)	0.80	(0.48–1.33)
Q3	0.67	(0.44–1.03)	0.91	(0.55–1.48)
Q4	0.74	(0.49–1.13)	0.59	(0.34–1.00)
P for trend		0.12		0.09
Carbohydrate[c] (%)				
Q1	1.00		1.00	
Q2	0.98	(0.62–1.56)	0.98	(0.56–1.13)
Q3	1.05	(0.65–1.71)	1.26	(0.71–2.26)
Q4	0.89	(0.89–1.52)	1.11	(0.59–2.09)
P for trend		0.75		0.59
Fat[c] (%)				
Q1	1.00		1.00	
Q2	0.86	(0.56–1.31)	1.10	(0.65–1.85)
Q3	0.81	(0.53–1.26)	0.76	(0.44–1.32)
Q4	0.58	(0.36–0.93)	0.77	(0.44–1.34)
P for trend		0.02		0.21
Protein[c] (%)				
Q1	1.00		1.00	
Q2	0.71	(0.47–1.07)	0.72	(0.43–1.20)
Q3	0.63	(0.41–0.96)	0.83	(0.50–1.36)
Q4	0.51	(0.33–0.79)	0.55	(0.32–0.95)
P for trend		0.002		0.05

[a] Adjusted for age, income, smoking, green tea drinking (females only), and response status.
[b] Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.
[c] Also adjusted for total calories.

Discussion

A major finding of our case-control study in Shanghai was the reduced risks of pancreatic cancer with increasing consumption of fresh fruits and vegetables. This observation is consistent with several previous studies conducted mainly in Western countries (2–8). The lowered risks may be partly related to the antioxidant effects of micronutrients such as vitamins C and E and carotene, which are abundant in fruits and vegetables (32, 33). Vitamins C and E can also block the endogenous formation of *N*-nitroso compounds (34, 35), which are suspected to be pancreatic carcinogens in animal models (36, 37). The inverse associations we observed with dietary intake of vitamins C and E and carotene are consistent with other studies of pancreatic

Table 5 ORs[a] and 95% CIs of pancreatic cancer in relation to intake of selected micronutrients and fiber by sex, Shanghai, China, 1990–1993

		Men					Women				
		Q1[b] (low)	Q2	Q3	Q4 (high)	P for trend	Q1 (low)	Q2	Q3	Q4 (high)	P for trend
Vitamin C	OR	1.00	1.20	0.62	0.53	0.0008	1.00	1.10	0.79	0.66	0.07
	95% CI		(0.77–1.70)	(0.40–1.00)	(0.33–0.84)			(0.71–1.90)	(0.47–1.30)	(0.37–1.20)	
Carotene	OR	1.00	0.91	0.80	0.53	0.006	1.00	0.70	0.86	0.38	0.01
	95% CI		(0.61–1.40)	(0.52–1.20)	(0.34–0.83)			(0.43–1.10)	(0.53–1.40)	(0.20–0.71)	
Vitamin E	OR	1.00	0.87	0.56	0.57	0.006	1.00	1.30	1.20	0.81	0.56
	95% CI		(0.57–1.30)	(0.36–0.89)	(0.35–0.93)			(0.75–2.10)	(0.68–1.90)	(0.44–1.50)	
Retinol	OR	1.00	0.77	0.63	0.61	0.02	1.00	0.88	0.62	0.48	0.008
	95% CI		(0.51–1.20)	(0.41–0.98)	(0.39–0.97)			(0.54–1.14)	(0.37–1.10)	(0.26–0.88)	
Fiber	OR	1.00	0.66	0.60	0.53	0.01	1.00	0.73	0.79	0.67	0.26
	95% CI		(0.43–1.00)	(0.38–0.94)	(0.32–0.89)			(0.44–1.10)	(0.46–1.40)	(0.36–1.30)	

[a] Adjusted for age, income, smoking, green tea drinking (females only), response status, and total calories.
[b] Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

cancer (2–6, 20, 23). However, the protective effects of other constituents of fruits and vegetables need to be explored (33, 34). One such factor may be fiber, which was inversely associated with pancreatic cancer in our study, as well as others (21–23, 38). It is not clear whether fiber itself is protective or whether it is merely a marker of fruit and vegetable intake (22). Other components of fruits and vegetables may be protective as well, including isoflavones, protease inhibitors, and phytosterols, which are concentrated in soybeans and other legumes (33, 39, 40). However, our results did not support previous suggestions that soybean products may inhibit the development of pancreatic cancer (41, 42).

A new finding was the excess risk associated with consumption of preserved vegetables, which contain large quantities of nitrites and nitrates that may serve as substrates for endogenous formation of *N*-nitroso compounds (36). However, we found no excess risk associated with preserved animal foods, which are also rich in nitrites and nitrosamines (43). Unlike preserved vegetables, preserved animal foods in China are relatively expensive specialty items, and the past consumption levels may have been too low to affect pancreatic cancer risk. Alternatively, risk factors correlated with aspects of socioeconomic status, even after adjustment for income and smoking, may confound the excess risk associated with consumption of preserved vegetables, and possibly the reduced risks we observed with intake of preserved and fresh animal foods.

We also found an increased risk of pancreatic cancer in relation to frequent consumption of deep-fried or grilled foods, in accord with a case-control study in Sweden, suggesting an association with grilled or fried meat (4). It is of interest to note that fat intake *per se* is not a risk factor in our study, suggesting that the cooking process may be an important factor. High-temperature cooking of meat may produce a variety of mutagens and carcinogens, including polycyclic aromatic hydrocarbons and heterocyclic aromatic amines (44, 45), although their effects on pancreatic carcinogenesis remain unclear (46, 47). Elevated risks were associated also with frequent consumption of cured or smoked foods, which are high in nitrites and nitrosamines (37, 48). The number of subjects who often consumed these food items was relatively small.

The inverse associations we observed with intake of calories, fat, and protein were unexpected. Most studies have reported positive associations with consumption of calories, fat, and meat (3, 5, 9–11, 15–18, 20, 23). The few exceptions include reports of reduced risks with egg consumption (3, 11, 49), as noted also in our study, and with intake of beef (2), total fat (19, 23), and unsaturated fat (20, 21, 24). All of these studies were conducted in Western countries where consumption of fat and meat has contributed a much higher proportion of total calories than in China (50). In the United States, over 40% of calories is derived from dietary fat (51), *versus* an average of 21% of calories from fat in Shanghai. It is possible that the average fat intake for Shanghai residents did not reach the threshold to affect pancreatic cancer risk, or that intake of certain fats may be protective, as suggested in some animal models. For example, Syrian hamsters fed a diet rich in linoleic acid have an increased resistance to pancreatic injury by trypsin and bile infused into the common bile duct (52). In rats, a diet rich in omega-3 fatty acid has been shown to inhibit development of pancreatic cancer (53). Polyunsaturated fatty acids also limit the growth of human pancreatic cancer cells *in vitro* (54). On the other hand, subjects who can afford frequent consumption of fresh and preserved meat may have protective lifestyle elements that remained to be identified. Despite several reports linking high carbohydrate intake to pancreatic cancer risk (17, 20, 22, 23), we found no association with carbohydrates. However, given the increasing availability in Shanghai of a wide variety of foods, including meat and other high-fat items, further study of dietary and nutritional risk factors for pancreatic cancer appears warranted (55).

Several strengths and limitations of this study should be considered in interpreting the results. It is one of the largest case-control studies of pancreatic cancer, and the first conducted in China. Our recruitment of over 78% of eligible cases represents a relatively successful field effort. However, substantial numbers of case (38%) and control (10%) interviews were assisted by next of kin. All results were adjusted accordingly, and exclusion of subjects whose interviews were assisted by next of kin did not alter the study findings. Whereas the majority of cases had histological confirmation or surgery, 43% were diagnosed only by computed tomography scan/ultrasound. However, our findings were not affected by the diagnostic status of cases. Approximately 19% of the identified cases were not interviewed, mainly due to death, thus raising the possibility of survival bias. If risk factors were more prevalent among the deceased, this exclusion would bias our results toward the null. Selection bias seems unlikely because of the low refusal rate and high personal interview rate. In addition, gastrointestinal and other symptoms before pancreatic cancer diagnosis may alter the dietary pattern of a patient, which, in turn, may influence recall and reporting of usual diet 5 years before diagnosis (56). The direction and extent of recall bias, if any, may be influenced by the type of symptoms and general condition of the patient before diagnosis. However, given the rapidly progressive nature of pancreatic cancer, patients might not have altered their dietary habits very long before diagnosis, so that recall bias of dietary habits should not be a major problem.

In summary, this large population-based case-control study of pancreatic cancer in Shanghai has confirmed epidemiological observations in Western countries of a protective effect of fruits and vegetables and certain components such as vitamins C and E, carotene, and dietary fiber. However, we did not find positive associations with intake of fat, protein, or carbohydrates that have been reported in some studies. In our study, excess risks were linked to frequent consumption of preserved vegetables and deep-fried, grilled, cured, or smoked foods, providing clues to the possible role of nitrosamines, polycyclic aromatic hydrocarbons, and heterocyclic aromatic amines. The pattern of dietary risk factors in our study suggests that variations in the diet have contributed little to the upward trends in pancreatic cancer, which appear to be strongly influenced by smoking (26) and perhaps by improvements in diagnosis and reporting. However, given the improving food availability and recent dietary changes in China, further studies will be needed to clarify the dietary and nutritional determinants of pancreatic cancer.

Appendix 1 Compositions of food groups

Food group or item	Composition
Preserved vegetables	Salted, moldy, dried vegetables; salted vegetables, hot pickled mustard stem; fermented bean-curd
Preserved animal food	Sausages, salted egg, preserved limed duck eggs, salted pork, salted fish
Fred red meats	Pork chops, pork spareribs, pork feet, fresh pork (fat), fresh pork (lean), fresh pork (fat and lean), pork liver, other organ meats, beef and mutton
Organ meats	Pork liver, other organ meats
Fish	Salt water fish (*e.g.*, hairtail, yellow croaker), fresh water fish (*e.g.*, silver carp, golden carp), eel
Poultry	Chicken, duck
Eggs	Fresh poultry eggs, salted eggs, limed duck eggs
Staple foods	Rice, noodle, steamed bun
All vegetables	Shanghai bok choy, spinach, cabbage, Chinese cabbage, cauliflower, celery, bean sprouts, eggplant, wild rice stem, pea pods, geeen peas, geeen bean, green broad beans, celtuce, potato, white gourd, cucumber, carrot, dried mushrooms, fresh mushrooms, red and green pepper, tomato, bamboo shoot, lotus root, luffa or sponge gourd, garlic, onion, Chinese chives, spring onion, corn, garlic stalks, ginger, kelp and seaweeds
Dark geeen leafy vegetables	Spinach, Chinese chives, spring onion
Cruciferous vegetables	Shanghai bok choy, cabbage, Chinese cabbage, cauliflower
Legumes	Soy bean/red bean, mung beans, other dried beans, peanuts, green peas, fresh fava beans (or green broad beans)
Soybean products	Bean curd, soybean milk, textured soybean products
All fruits	Apple, pear, orange/tangerine, banana, grape
Other fruits	Grape, pear

Appendix 2 Cutpoints for quartiles (Q1, Q2, Q3, Q4) of servings of food group per month (by sex)

Food group/item	Sex	Quartile			
		Q1 (low)	Q2	Q3	Q4 (high)
Preserved vegetables	Men	≤2.3	2.4–6.3	6.4–13.9	≥14.0
	Women	≤2.8	2.9–6.4	6.5–13.1	≥13.2
Preserved animal food	Men	≤1.6	1.7–2.8	2.9–7.2	≥7.3
	Women	≤1.3	1.4–2.8	2.9–7.2	≥7.3
Fresh red meats	Men	≤13.7	13.8–22.5	22.6–37.7	≥37.8
	Women	≤10.7	10.7–19.8	19.9–33.1	≥33
Organ meats	Men	0	0.1–0.3	0.4–1.1	≤1.2
	Women	0	0.1–0.2	0.3–1.0	≥1.1
Fish	Men	≤2.6	2.7–5.0	5.1–9.3	≥9.4
	Women	≤2.9	3.0–5.4	5.5–10.9	≥11.0
Poultry	Men	≤0.5	0.6–1.3	1.4–2.8	≥2.9
	Women	≤0.5	0.6–1.1	1.2–2.0	≥2.1

Appendix 2 Continued

Food group/item	Sex	Quartile			
		Q1 (low)	Q2	Q3	Q4 (high)
Eggs	Men	≤7.4	7.5–13.9	14.0–22.3	≥22.6
	Women	≤6.5	6.6–13.8	13.9–25.4	≥22.5
Staple foods	Men	≤93.0	93.1–97.3	97.4–104.9	≥105.0
	Women	≤93.0	93.1–96.3	96.4–102.9	≥103.0
All vegetables	Men	≤68.6	68.7–92.0	92.1–122.1	≥122.2
	Women	≤66.7	66.8–91.9	92.0–118.5	≥118.6
Green leafy vegetables	Men	≤2.3	2.4–4.6	4.7–10.4	≥10.5
	Women	≤2.3	2.4–4.1	4.2–10.1	≥10.2
Cruciferous vegetables	Men	≤15.0	15.1–22.3	22.4–25.3	≥25.4
	Women	≤15.7	15.8–22.4	22.5–25.7	≥25.8
Legumes	Men	≤4.1	4.2–8.8	8.9–20.0	≥20.1
	Women	≤3.7	3.8–7.8	7.9–18.6	≥18.7
Soybean products	Men	≤8.0	8.1–13.1	13.2–25.7	≥25.8
	Women	≤7.0	7.1–12.9	13.0–22.4	≥22.5
All fruits	Men	≤1.7	1.8–5.7	5.8–14.6	≥14.7
	Women	≤2.1	2.2–7.1	7.2–16.4	≥16.5
Oranges/tangerines	Men	≤2.0	2.1–3.0	3.1–3.9	≥4.0
	Women	≤2.0	2.1–3.0	3.1–3.9	≥4.0
Bananas	Men	≤2.0	2.1–3.0	3.1–4.0	≥4.1
	Women	≤2.0	2.1–3.0	3.1–4.0	≥4.1
Apples	Men	≤2.0	2.1–3.0	3.1–4.0	≥4.1
	Women	≤2.0	2.1–3.0	3.1–3.9	≥4.0
Other fruits	Men	≤0.5	0.6–1.2	1.3–4.4	≥4.5
	Women	≤0.5	0.6–1.2	1.3–4.3	≥4.4

Appendix 3 Cutpoints for quartiles (Q1, Q2, Q3, Q4) of nutrient intake per day[a] (by sex)

Nutrient (unit)	Sex	Quartile			
		Q1 (low)	Q2	Q3	Q4 (high)
Total calories (kcal)	Men	≤2157.7	2157.8–2540.3	2540.4–2931.4	≥2931.5
	Women	≤1777.4	1777.5–2097.2	2097.3–2442.1	≥2442.2
Total carbohydrate (%)	Men	≤61.9	62.0–67.1	67.2–71.6	≥71.7
	Women	≤61.4	61.5–67.0	67.1–71.3	≥71.4
Total fat (%)	Men	≤17.1	17.2–21.0	21.1–25.7	≥25.8
	Women	≤17.5	17.6–21.1	21.2–25.5	≥25.6
Total protein (%)	Men	≤10.5	10.6–11.7	11.8–13.1	≥13.2
	Women	≤10.2	10.3–11.6	11.7–13.2	≥13.3
Vitamin C (mg)	Men	≤22.9	30.0–41.6	41.7–57.1	≥57.2
	Women	≤28.9	29.0–41.2	41.3–42.3	≥42.4
Carotene (mg)	Men	≤447.3	447.3–677.8	677.9–1045.3	≥1045.4
	Women	≤465.8	465.9–639.1	639.2–1039.2	≥1039.3
Vitamin E (TE)[b]	Men	≤26.1	26.2–31.8	31.9–40.8	≥40.9
	Women	≤24.1	24.2–29.1	29.2–37.1	≥37.2
Retinol (RE)[c]	Men	≤176.0	176.1–269.1	269.2–402.8	≥402.9
	Women	≤163.7	163.8–242.0	242.0–366.5	≥366.6
Fiber (g)	Men	≤7.0	7.1–9.0	9.1–12.3	≥12.4
	Women	≤6.0	6.1–7.7	7.8–10.4	≥10.5

[a] Monthly intake was converted to intake per day for ready comparison with other publications.
[b] TE, milligram of α-tocopherol (1 TE = 1.5 IU).
[c] RE, retinal equivalent.

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